

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
20 September 2001 (20.09.2001)

PCT

(10) International Publication Number
WO 01/67864 A2

(51) International Patent Classification⁷: **A01N 59/08, 25/30, A61K 33/14, 9/00 // (A01N 59/08, 59/26, 59/02, 37/04)**

(21) International Application Number: **PCT/GB01/01121**

(22) International Filing Date: **15 March 2001 (15.03.2001)**

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:
0006243.0 15 March 2000 (15.03.2000) GB
0007327.0 28 March 2000 (28.03.2000) GB

(71) Applicant (for all designated States except US): **NORTON HEALTHCARE LTD. [GB/GB]**; Albert Basin, Royal Docks, London E16 2QJ (GB).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **BERKOWITZ, Joshua [ZA/GB]**; 3 Laurimel Close, Stanmore, London HA7 2SU (GB).

(74) Agent: **BROWNE, Robin, Forsythe; Urquhart-Dykes & Lord, Tower House, Merrion Way, Leeds LS2 8PA (GB)**.

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/67864 A2

(54) Title: **TOPICAL VIRUCIDAL FORMULATION**

(57) Abstract: A topical virucidal pharmaceutical formulation comprising as active ingredient an inorganic halide, an oxidising agent capable of generating hypohalite ions in aqueous solution, a sulphamic acid, a non-reducing organic acid and an inorganic phosphate optionally with a surfactant, preferably an anionic surfactant, together with one or more pharmaceutically acceptable excipients.

TOPICAL VIRUCIDAL FORMULATION

This invention relates to a topical virucidal formulation, particularly but not exclusively to a cream or other solid formulation for eradication or treatment of viral infections particularly on the skin or mucous membranes. The formulation may be used for therapeutic or prophylactic purposes. The invention also relates to ointments, pastes, emulsions, gels and rigid foam formulations.

A virucidal disinfectant composition for use with surgical equipment is disclosed in GB-A-2164851. This comprises an oxidising agent, for example potassium persulphate, sodium chloride, sulphamic acid, a non-reducing organic acid, an acid pyrophosphate and an anionic surfactant. Such disinfectants are sold under the trade mark VIRKON. There is no disclosure that this composition may be used in a pharmaceutical formulation.

According to a first aspect of the present invention a topical virucidal pharmaceutical formulation comprises as active ingredients an inorganic halide and an oxidising agent capable of generating hypohalite ions in aqueous solution, a sulphamic acid, a non-reducing organic acid and an inorganic phosphate optionally with a surfactant, preferably an anionic surfactant, together with one or more pharmaceutically acceptable excipients.

According to a second aspect of the present invention there is provided use of a composition for manufacture of a topical virucidal formulation, the composition comprising as ingredients an inorganic halide and an oxidising agent capable of generating hypohalite ions in aqueous solution; a sulphamic acid, a non-reducing organic acid and an inorganic phosphate optionally with a surfactant, preferably an anionic surfactant, together with one or more pharmaceutically acceptable excipients.

The oxidising agent is preferably a persulphate or pyroxiphthalate, particularly potassium persulphate. The inorganic halide is preferably sodium chloride.

The non-reducing organic acid may be selected from: malic acid, succinic acid and mixtures thereof.

The phosphate may be selected from disodium hydrogen pyrophosphate or potassium dihydrogen phosphate. Alternative anhydrous phosphates may be employed.

-2-

Any compatible pharmaceutically acceptable surfactant may be employed, for example sodium dodecylbenzene sulphonate, lauryl ethyl sulphonate and polyethylene oxide/polypropylene oxide condensates.

A preferred formulation available under the trade mark VIRKON comprises

potassium persulphate (triple salt)	50%
sodium chloride	15%
sulphamic acid	5%
malic acid	10%
disodium pyrophosphate	5%
anionic surfactant	15%
	100%

The amount of the ingredients containing the active moieties is preferably a minimum amount necessary to provide virucidal efficacy. An amount of 0.1% to 40%, preferably 0.2% to 5%, preferably 1 to 3% by weight may be employed. Amounts and proportions in this specification are by weight unless otherwise indicated otherwise.

The formulation may comprise a cream wherein particles of the active-containing ingredients are uniformly dispersed. In order to ensure homogeneity of the product the particles may have a dimension less than 75 μm to provide a smooth cream having good dermal contact.

The formulation may include a hydrocarbon base, for example petrolatum or white ointment. An absorption base may be added, for example lanolin, lanolin isolates, cholesterol, lanosterol, acylated sterols or partial esters of polyhydric alcohols for example sorbitan monostearate or monooleate, or mixtures thereof.

Water removable bases are preferred to facilitate removal of the cream from the skin or clothing.

Creams in accordance with the present invention may incorporate one or more emulsifiers optionally together with one or more co-emulsifiers for example cetyl alcohol or glyceryl monostearate. Polyvalent ions, for example magnesium, calcium or aluminium may be added to stabilise the emulsion. A mixed emulsifier system maybe employed.

-3-

A humectant, for example glycerin, propyleneglycol or sorbitol may be employed to prevent drying of the cream on storage.

Formulations of the present invention find particular application as a prophylactic treatment for HIV or hepatitis infections for example as a vaginal cream or as a lining for surgical, dental, other medical or veterinary gloves

An advantage arising from use of the present formulation is that the formulation is pink in colour. Loss of the pink colour before or during use indicates a loss of activity.

The invention is further described by means of example but not in any limitative sense.

Example 1

A formulation was prepared using the following ingredients:

Aqueous cream BP	495 g
Virkon	5 g
<hr/>	
	500 g

The resultant formulation was a pink cream.

Example 2

A formulation was prepared using:

Aqueous cream BP	97.5 g
Virkon	2.5 g
<hr/>	
	100 g

The resultant formulation was a pink cream. Tests were carried out to determine virucidal activity. Hepatitis A virus was used on account of its known resistance to virucides. The cream showed excellent efficacy.

CLAIMS

1. A topical virucidal pharmaceutical formulation comprising as active ingredient an inorganic halide, an oxidising agent capable of generating hypohalite ions in aqueous solution, a sulphamic acid, a non-reducing organic acid and an inorganic phosphate optionally with a surfactant, preferably an anionic surfactant, together with one or more pharmaceutically acceptable excipients.
2. A formulation as claimed in claim 1, wherein the oxidising agent is selected from the group consisting of persulphate and pyroxiphthalate.
3. A formulation as claimed in claim 2, wherein the oxidising agent is potassium persulphate.
4. A formulation as claimed in any preceding claim, wherein the non-reducing organic acid is selected from the group consisting of: malic acid, succinic acid and mixtures thereof.
5. A formulation as claimed in any preceding claim, wherein the phosphate is selected from the group consisting of disodium hydrogen phosphate and potassium dihydrogen phosphate.
6. A formulation as claimed in any preceding claim, wherein the surfactant is selected from the group consisting of sodium dodecylbenzene sulphonate, lauryl ethyl sulphonate and polyethylene oxide/polypropylene oxide condensates.
7. A formulation as claimed in any preceding claim, wherein the active ingredient consists of:

potassium persulphate (triple salt)	50%
sodium chloride	15%
sulphamic acid	5%

-5-

malic acid	10%
disodium pyrophosphate	5%
anionic surfactant	15%
<hr/>	
	100%

8. A formulation as claimed in any preceding claim, comprising 0.1 to 40% of active ingredient.

9. A formulation as claimed in any preceding claim, comprising 0.2 to 5% of active ingredient.

10. A formulation as claimed in any preceding claim, comprising 1 to 3% of active ingredient.

12. A formulation as claimed in any preceding claim, comprising a cream wherein particles of active ingredient have a dimension less than 75 μm .

13. A formulation as claimed in any preceding claim, comprising a cream including a hydrocarbon base.

14. A formulation as claimed in claim 13, further comprising an absorption base selected from the group consisting of lanolin, lanolin isolates, cholesterol, lanosterol, acylated sterols and partial esters of polyhydric alcohols.

15. A formulation as claimed in claim 13 or 14, comprising a cream incorporating one or more emulsifiers optionally together with one or more co-emulsifiers.

16. A hand cream comprising a formulation as claimed in any of claims 13 to 15.

-6-

17. A coating for an internal surface of a surgical, dental, veterinary or other medical glove comprising a formulation as claimed in any of claims 1 to 15.

18. A vaginal cream comprising a formulation as claimed in any of claims 1 to 15.

19. A surgical glove having a coating of a formulation as claimed in any of claims 1 to 15 on an internal surface thereof.

20. Use of a composition for manufacture of a topical virucidal formulation, the composition comprising a formulation as claimed in any of claims 1 to 15.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
20 September 2001 (20.09.2001)

PCT

(10) International Publication Number
WO 01/067864 A3

(51) International Patent Classification⁷: A01N 59/08. (25/30, A61K 33/14, 9/00 // (A01N 59/08, 59:26, 59:02, 37:04)

(21) International Application Number: PCT/GB01/01121

(22) International Filing Date: 15 March 2001 (15.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0006243.0 15 March 2000 (15.03.2000) GB
0007327.0 28 March 2000 (28.03.2000) GB

(71) Applicant (for all designated States except US): NORTON HEALTHCARE LTD. [GB/GB]; Albert Basin, Royal Docks, London E16 2QJ (GB).

(72) Inventor; and

(73) Inventor/Applicant (for US only): BERKOWITZ, Joshua [GB/GB]; 3 Laurimel Close, Stanmore, London HA7 2SU (GB).

(74) Agent: WRIGHT, Robert, Gordon, McRae; Elkington and Fife, Prospect House, 8 Pembroke Road, Sevenoaks, Kent TN13 1XR (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
4 July 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/067864 A3

(54) Title: TOPICAL VIRUCIDAL FORMULATION

(57) Abstract: A topical virucidal pharmaceutical formulation comprising as active ingredient an inorganic halide, an oxidising agent capable of generating hypohalite ions in aqueous solution, a sulphamic acid, a non-reducing organic acid and an inorganic phosphate optionally with a surfactant, preferably an anionic surfactant, together with one or more pharmaceutically acceptable excipients.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/01121

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A01N59/08 A01N25/30 A61K33/14 A61K9/00 // (A01N59/08, 59;26, 59;02, 37:04)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 187 098 A (AUCHINCLOSS THOMAS R) 3 September 1987 (1987-09-03) page 1, line 39 -page 2, line 54 page 3, line 25 page 6, line 39 -page 7, line 2; claims ---	1-4, 6, 8-10, 20
X	GB 2 164 851 A (AUCHINCLOSS THOMAS R) 3 April 1986 (1986-04-03) cited in the application page 1, line 61 -page 3, line 12 Test 1 claims ---	1-10, 20
Y	US 5 262 174 A (HORROBIN DAVID F) 16 November 1993 (1993-11-16) column 1, line 16 - line 18 column 2, line 52 - line 63; examples ---	11-19
Y	US 5 262 174 A (HORROBIN DAVID F) 16 November 1993 (1993-11-16) column 1, line 16 - line 18 column 2, line 52 - line 63; examples ---	11-16
		-/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

13 November 2001

Date of mailing of the international search report

21/11/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Muellners, W

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/GB 01/01121

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 965 610 A (ADVANI BALRAM H ET AL) 12 October 1999 (1999-10-12) column 1, line 18 - line 29 column 3, line 10 - line 51 column 9, line 47 - line 61 column 10, line 40 - line 60 column 11, line 21 - line 32; examples 10-12, 19, 25-37 column 24, line 62 -column 25, line 5 -----	17-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/GB 01/01121

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
GB 2187098	A	03-09-1987	CA ZA AU AU DK EP WO JP JP US AT DE KR	1290243 A1 8708195 A 590950 B2 7659387 A 570887 A 0260293 A1 8705187 A1 5033921 B 63502662 T 4822512 A 55675 T 3764435 D1 9200863 B1	08-10-1991 02-05-1988 23-11-1989 09-02-1989 30-10-1987 23-03-1988 11-09-1987 20-05-1993 06-10-1988 18-04-1989 15-09-1990 27-09-1990 30-01-1992
GB 2164851	A	03-04-1986	JP JP JP	1873770 C 5088201 B 61165309 A	26-09-1994 21-12-1993 26-07-1986
US 5262174	A	16-11-1993	AT AU AU CA DE EP HK US US ZA	48945 T 578031 B2 3120484 A 1218931 A1 3480828 D1 0135312 A2 127693 A 4886670 A 5080909 A 8405833 A	15-01-1990 13-10-1988 12-09-1985 10-03-1987 01-02-1990 27-03-1985 26-11-1993 12-12-1989 14-01-1992 27-03-1985
US 5965610	A	12-10-1999	US AU AU CA EP JP WO US ZA	6037386 A 703926 B2 2195595 A 2184828 A1 0788305 A1 9510976 T 9526134 A1 5708023 A 9502521 A	14-03-2000 01-04-1999 17-10-1995 05-10-1995 13-08-1997 04-11-1997 05-10-1995 13-01-1998 15-03-1996